REMARKS

Claims 62-70, 73-78, 81-88, 91-99, 135, and 136 are pending in the application. Claim 70 is amended to provide clear antecedent basis. Claim 81 also is amended for purposes of clarity. No new matter is introduced.

As an initial matter, Applicants submit herewith a Supplemental Information Disclosure Statement and request consideration thereof by the Examiner. Applicants also request consideration of the Supplemental Information Disclosure Statement submitted May 5, 2008.

The pending claims are rejected under 35 U.S.C. § 103 for alleged obviousness over Borrebaeck *et al.*, *Adv. Drug Delivery Rev.*, 1988, 2:143-165, in view of Yelton *et al.*, *J. Immunol.*, 1995, 155:1994-2004, Zan *et al.*, *Immunity*, 2001, 14:643-653, and WO02/054856. Applicants disagree with the rejection.

Under 35 U.S.C. § 103, "the scope and content of prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented." *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1734 (2007) (citing *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966)). The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results. *Id.* at 1739. Obviousness rejections, however, "cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *Id.* at 1741.

This is not a case in which familiar elements are combined according to known methods to yield a predictable result. Claim 62 recites methods for producing hybridoma cells producing antibodies from *in vitro* immunized immunoglobulin-producing cells comprising: (a) combining donor cells comprising immunoglobulin-producing cells with an immunogenic antigen *in vitro*; (b) fusing said immunoglobulin-producing cells with myeloma cells to form parental hybridoma cells; (c) incubating said parental hybridoma cells in the

presence of at least one chemical inhibitor of mismatch repair, thereby forming hypermutated hybridoma cells; (d) screening antibodies produced from said hypermutated hybridoma cells for binding to antigen; and (e) selecting hypermutated hybridoma cells that produce antibodies with higher affinity for said antigen than antibodies produced by said parental hybridoma cells; thereby producing hybridoma cells producing antibodies having higher affinity for said antigen than antibodies produced by said parental hybridoma cells. Claim 73 recites methods for producing hybridoma cells that produce antibodies from *in vitro* immunized immunoglobulin-producing cells comprising: (a) combining donor cells comprising immunoglobulin-producing cells with an immunogenic antigen *in vitro*; (b) fusing said immunoglobulin-producing cells with myeloma cells to form parental hybridoma cells; (c) incubating said parental hybridoma cells in the presence of at least one chemical inhibitor of mismatch repair, thereby forming hypermutated hybridoma cells; and (d) selecting hypermutated hybridoma cells that produce higher titers of antigen-specific antibodies than said parental hybridoma cells; thereby producing hybridoma cells that produce higher titers of antibodies than said parental hybridoma cells. Claim 81 recites methods for producing mammalian expression cells that produce antibodies from *in vitro* immunized immunoglobulin-producing cells comprising: (a) combining donor cells comprising immunoglobulin-producing cells with an immunogenic antigen *in vitro*; (b) fusing said immunoglobulin-producing cells with myeloma cells to form hybridoma cells; (c) performing a screen for binding of antibodies produced from said hybridoma cells to antigen; (d) cloning immunoglobulin genes from hybridoma cells that produce antibodies to said antigen into a mammalian expression cell; (e) incubating said mammalian expression cell in the presence of at least one chemical inhibitor of mismatch repair, thereby forming hypermutated mammalian expression cells; (f) performing a screen for hypermutated mammalian expression cells that secrete antibodies with higher affinity for antigen as compared to antibodies produced from said hybridoma cells that produce antibodies to said antigen; thereby producing mammalian expression cells that produce antibodies having higher affinity for said antigen than said hybridoma cells that produce antibodies to said antigen from *in vitro* immunized immunoglobulin-producing cells. Claim 91 recites methods for producing mammalian expression cells that produce antibodies to a selected antigen from *in vitro* immunized immunoglobulin-producing cells comprising: (a) combining donor cells

comprising immunoglobulin-producing cells with an immunogenic antigen *in vitro*; (b) fusing said immunoglobulin-producing cells with myeloma cells to form parental hybridoma cells; (c) incubating said parental hybridoma cells in the presence of at least one chemical inhibitor of mismatch repair to form hypermutated hybridoma cells; (d) performing a screen for binding of antigen for antibodies produced from said hypermutated hybridoma cells; (e) selecting hypermutated hybridoma cells that produce antibodies with higher affinity for said antigen than antibodies produced by said parental hybridoma cells; (f) cloning immunoglobulin genes from said hypermutated hybridoma cells that produce antibodies with higher affinity for said antigen than antibodies produced by said parental hybridoma cells into a mammalian expression cell, thereby forming parental mammalian expression cells; thereby producing mammalian expression cells that produce antibodies having higher affinity for said antigen than said parental hybridoma cells from *in vitro* immunized immunoglobulin-producing cells.

In vivo antibody maturation occurs in a multi-step process. The Borrebaeck reference states that "[t]he humoral response to antigens implicates the activation and proliferation of immunoglobulin-bearing B cells and their subsequent maturation into an antibody-producing stage.... Study of the B cell activation process reveals the presence of three distinct steps: induction/activation, proliferation, and differentiation." Borrebaeck reference, page 144. "In vitro immunization should therefore parallel the antigen-specific activation in vivo." Borrebaeck reference, page 145. Indeed, the Examiner states on page 3 of the Action that "[i]t would have been prima facie obvious at the time the claimed invention was made to transiently *expose hybridoma cells* from in vitro immunized lymphocytes *to chemical inhibitors of mis-match repair* as taught by Nicolaides et al *in order to mimic affinity maturation in vivo* and obtain higher affinity antibodies and thus higher titer antibodies." The Examiner further states that the Zan reference teaches that B cells contain trans-lesion polymerases that include error prone polymerases (mis-pair inserters) and polymerases able to extend DNA chains from a mis-pair and that "one of skill in the art would understand that the inhibitors of Nicolaides et al would increase the rate of mutations inserted by the by-pass polymerases and thus provide for a higher rate of somatic mutations and the accumulation of a population of somatic mutants allowing for the selection of higher affinity antibodies formed as a result of said somatic mutation." Office Action pages 3-4. Applicants disagree.

According to Cascalho *et al.*, *Science*, 279:1207-1210, 1998, submitted herewith, "mismatch repair seems to *contribute* to somatic hypermutation rather than stifling it." Cascalho reference, abstract (emphasis added). Thus, the Cascalho references teaches that somatic hypermutation may be facilitated by mismatch repair; thus inhibitors of mismatch repair would be expected to have the opposite effect. One skilled in the art seeking to mimic *in vivo* antibody maturation conditions in accordance with the Borrebaeck reference thus would not inhibit mismatch repair in view of the teaching by the Cascalho reference that somatic hypermutation may be facilitated by mismatch repair.

Additionally, the Borrebaeck and Yelton references teach away from the combination with chemical inhibitors of mismatch repair described by WO02/054856. The Borrebaeck reference states that:

> There are still a number of parameters that are under investigation ... before a human in vitro immunization system is fully optimized. The most important development will, however, take place in the area of antibody engineering. Although the "humanizing" of mouse monoclonal antibodies has its limitation regarding antibody specificity ... changing isotypes and regulating antibody affinities and specificities will be important technologies when applied to human monoclonal antibodies. To obtain the optimal isotype and affinity of therapeutically valuable human monoclonal antibodies we need to be able to "tailor make" specific changes on pre-formed human hybridomas produced by in vitro immunization. This change in affinity/specificity and of isotype can be performed by site-directed mutagenesis, and construction of chimeric antibodies, or long-term in vitro culture of normal antigen-specific activated B cells....

Borrebaeck reference, pages 159-160. Thus, the Borrebaeck reference teaches that antibody optimization requires the ability to "tailor make" specific changes. The Examiner cites the Yelton reference for its demonstration of the "desirability of exploiting in vitro immunized antibodies to obtain high affinity antibodies." Office Action, page 3. The Yelton reference describes codon-based mutagenesis as a strategy for mutating antibodies to improve function. Yelton reference, page 1995. The Yelton reference further states that "[m]utagenic methods such as error-prone PCR or chemical mutagenesis are less efficient for introducing all possible substitutions at a given position, and generally introduce mutations over an entire V region." Yelton reference, page 1995. Inhibition of mismatch repair in accordance with the presently claimed methods would induce accumulation of genome-wide point mutations

rather than site-specific alterations. See Specification, paragraph 0126. Thus the references cited by the Examiner in fact teach away from the present invention.

Because this is not a case in which familiar elements are combined according to known methods to yield a predictable result and because the art teaches away from the present invention, withdrawal of the rejection for alleged obviousness is respectfully requested.

Conclusion

Applicants believe that the foregoing constitutes a complete and full response to the Office Action of record. Accordingly, an early and favorable Action is respectfully requested. Should any issues remain unresolved by the present remarks, the Examiner is invited to contact the undersigned at 215.568.3100.

Respectfully submitted,

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/ Felicity E. Groth /
Felicity E. Groth
Registration No. 47,042

Attachments
Supplemental Information Disclosure Statement

Woodcock Washburn LLP
Cira Centre
2929 Arch Street, 12th Floor
Philadelphia, PA 19104-2891
Telephone: (215) 568-3100
Facsimile: (215) 568-3439